THE HOPKINS HIV REPORT

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A Review of Dual Protease Inhibitor Therapy

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The Hopkins HIV Report - May 1998

The initial use of dual protease inhibitor (PI) regimens in clinical practice did not follow closely behind data from clinical trials. While early studies demonstrated the efficacy of ritonavir/saquinavir in PI-naive patients, most clinicians used this combination only as a salvage option after the failure of a single PI-containing regimen. Research on salvage therapy with dual PIs lagged far behind, but eventually confirmed th generally negative experience of clinicians forced to use these regimens for lack of better options.

Dual protease inhibitor regimens as initial therapy are attractive for a number of reasons. The combination of two powerful agents with differing resistance patterns offers the potential for greater efficacy and may pose more obstacles to drug failure. Many of these combinatior take advantage of pharmacokinetic interactions which lead to increased drug levels, reduced total daily pill burden, and decreased number daily doses. These regimens offer more reliable combination therapy for patients with extensive prior exposure to reverse transcriptase inhibitors. When dual PI regimens are taken without supplemental reverse transcriptase inhibitors, they may be less expensive than other combinations and may be associated with less toxicity. However, the trend has been to supplement these regimens with nucleoside or non-nucleoside reverse transcriptase (RT) inhibitors in most cases.

Dual-PI regimens also have several disadvantages. PI-related toxicity may be greater. This might include hepatotoxicity, especially in patien with chronic viral hepatitis. In addition, patients taking two PIs may be at greater risk for diabetes hyperlipidemia, or other metabolic abnormalities associated with PI therapy. Patients failing dual-PI regimens may also have more extensive cross-resistance and fewer salva options than those failing single agents. Since protease inhibitors do not penetrate the CNS, there is concern that such regimens may allow for the possibility of "CNS escape." However, as noted above, most patients taking dual-PI regimens take them with supplemental RT inhibitors, which may cross the blood-brain barrier.

Much of the data on dual protease inhibitor therapy from the recent Retrovirus Conference in Chicago was reviewed in the last issue of *The Hopkins HIV Report* [Vol. 10, No. 2, March 1998]. The following discussion will summarize what is known about specific dual-PI combinations.

Ritonavir/saquinavir (RTV/SQV)

This is the most extensively studied and most widely used dual protease inhibitor combination. Sixty-week data are now available from a tria involving over 100 patients, and in that trial 89% of patients continue to have undetectable viral loads (<200 copies/ml). Because the lower dose regimen (400/400 mg bid) was better tolerated and equally efficacious, all participants were allowed to switch to that regimen at 48 weeks.

The results of this trial led the DHHS guidelines committee to add RTV/SQV to the list of preferred protease inhibitors for initial therapy. The reduced dose of ritonavir is better tolerated than full-dose ritonavir (600 mg bid). This regimen is also more convenient than other saquinavir containing regimens, which now require that the patient take six capsules of saquinavir three times daily.

RTV/SQV is also the most widely used "salvage" regimen for patients failing therapy with other protease inhibitors. Several small retrospective studies looking at indinavir (IDV) failure suggest that RTV/SQV is rarely effective once IDV resistance has developed, a finding consistent with what is known about resistance patterns associated with IDV therapy. However, there are some data suggesting that RTV/SQV may be effective in patients who switch from IDV to RTV/SQV early. Switching when the viral load is low may minimize the numbe of mutations that lead to cross-resistance.

The experience with RTV/SQV after nelfinavir (NFV) failure has been somewhat more positive. In one study prolonged suppression of viral load was reported in up to two-thirds of patients failing NFV and switching to RTV-SQV containing regimens. These findings are consistent with what is known about genotypic patterns of NFV resistance, which is typically heralded by the development of the D30N mutation, a mutation which by itself does not lead to decreased susceptibility to other protease inhibitors. RTV/SQV also appears to be effective in a number of patients who fail therapy with SQV alone. In one study, switching from SQV to RTV/SQV was more effective than switching to either IDV or RTV alone. In another study, both RTV/SQV and IDV were effective following SQV failure. However, both studies involved failure of the hard-gel formulation of SQV (Invirase), for which drug failure may sometimes be due to low drug levels rather than resistance. These findings may not apply as well to failure of the soft-gel formulation (Fortovase).

When the soft-gel capsule formulation of SQV (Fortovase) is used in combination with RTV, the same dose (400 mg bid) leads to equivaler plasma concentrations as seen with the hard-gel formulation (Invirase) and costs significantly less.

Nelfinavir/saquinavir (NFV/SQV)

NFV increases the AUC of SQV by 5-fold, while SQV has no effect on NFV levels. In the European SPICE trial, more patients randomized t receive SQV (soft-gel formulation) 800 mg tid plus NFV 750 mg tid plus two nucleoside analogs had undetectable viral loads than those receiving the NFV/SQV alone or either of the two protease inhibitors plus two nucleosides. For salvage therapy, there is less experience wi this combination than with RTV/SQV. Because NFV has a more modest effect on SQV metabolism than RTV, the reduction in pill burden is minimal: the regimen used in the SPICE trial requires patients to take seven capsules three times daily, not including nucleoside analogs.

Ritonavir/nelfinavir (RTV/NFV)

In a single-dose pharmacokinetic trial, RTV increased the AUC of NFV by 2.5-fold. RTV may also accentuate the M8 metabolite of NFV, possibly resulting in increased antiviral activity. Data from a pilot trial involving RTV (400 mg bid) plus either 500 mg or 750 mg bid of NFV suggest that this combination has potent activity, but like NFV/SQV, may require supplemental reverse transcriptase inhibitors for optimal activity. Pharmacokinetic studies are in progress.

Ritonavir/indinavir (RTV/IDV)

A multidose pharmacokinetic study of this combination demonstrated that IDV clearance is reduced by RTV, which leads to less variability i pharmacokinetics and increased trough levels. At the 400/400 mg bid dose, the AUC of IDV approximates that of the standard dose of IDV (800 mg q8h), thus making IDV a bid medication. RTV may also reduce the effect of food on IDV. Efficacy data are not available for this combination.

Indinavir/nelfinavir (IDV/NFV)

In a single dose study, NFV increased the AUC of IDV by 50%, and IDV increased the AUC of NFV by 80%. Clinical trials of IDV/NFV are ir progress, but the right dose combination hasn't been worked out yet. Doses of 1000 mg and 750 mg bid of IDV and NFV, respectively, led t adequate trough levels of IDV but inadequate trough levels of NFV. The same was true when the dose of NFV was increased to 1000 mg bi Efficacy was disappointing, perhaps because of inadequate drug levels. Until appropriate dosing can be worked out, this combination shoul probably be avoided in clinical practice.

Indinavir/Saquinavir (IDV/SQV)

Despite a potentially favorable pharmacokinetic interaction, this combination has not been studied because of the demonstration of in vitro antagonism. It is not clear whether this antagonism is clinically relevant, but until this has been determined, the combination probably shoul not be used.

Amprenavir in Dual-PI Combinations

Amprenavir, the new Glaxo-Wellcome PI formerly known as 141W94, has been combined with SQV, IDV, and NFV in a small pilot study. Al combinations were well-tolerated and associated with significant viral suppression.

ABT-378/ritonavir

The new protease inhibitor from Abbott Laboratories, ABT-378, has in vitro potency ten times greater than that of RTV, and like RTV, is metabolized by the CYP3A pathway. In a placebo-controlled, multiple-dose study of ABT-378 plus RTV, high drug levels of ABT-378 were achieved when 200 to 600 mg bid were combined with 50 or 100 mg of RTV. Similar levels were also achievable with once daily dosing.

In summary, there is growing evidence to support the use of dual protease inhibitor regimens for the treatment of HIV disease. These regimens are most effective when taken in combination with reverse transcriptase inhibitors by patients who are treatment naive, or at least naive to protease inhibitors. Of the dual-PI regimens, RTV/SQV is the best studied combination, with excellent potency and durability, and it the only one to be listed as a preferred regimen in the DHHS guidelines. Although far from perfect, RTV/SQV (with new RT inhibitors) may s be the best "salvage regimen" for people failing regimens with single protease inhibitors. Initiating salvage therapy early, while the viral load low, may increase the chances of a successful response. The only other dual-PI regimen with established clinical efficacy in PI-naive patien is NFV/SQV. There is less support for use of NFV/SQV following failure of other PIs. All other dual-PI regimens are under study, and shoulc be used with caution, if at all, until further data are available on safety, pharmacokinetics, and efficacy.

Dual-PI regimens may be capable of profound and extremely durable suppression of viral replication. RTV/SQV may, in fact, be the most potent antiretroviral regimen currently available. However, dual-PI regimens should be used with caution in patients who may have trouble adhering to antiretroviral therapy. Resistance to dual-PI combinations is likely to lead to extensive cross-resistance within the PI class. The choice to initiate therapy with two protease inhibitors may involve a decision to sacrifice "salvageability" for the sake of potency and durabili Patients who make this choice must do everything they can to make the regimen last.

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